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THE EFFECT OF TIME OF DAY, THE TEST-RETEST RELIABILITY AND THE RELATIONSHIP OF GAIT OUTCOME MEASURES WITH FATIGUE IN PERSONS WITH MULTIPLE SCLEROSIS

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MSc. (Post-registration) In Advancing Physiotherapy Practice

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Abstract

One of the biggest challenges persons with multiple sclerosis (pwMS) are facing is difficulty in walking and this is related to decrease in quality of life (QOL). The throughout day variability of walking capacity and everyday unpredictability of symptoms, along with perceptions of fatigue may be related to the reduced walking ability and participation in functional activity.

Aims and Hypotheses:

The aims were to analyse the effect of time of day on walking and determine the between-day retest reliability of the tested 3D gait kinematics analysis and the 10-meter (10mWT) walking performance test. This study also aimed to determine the correlation between perceived fatigue severity (Fatigue Severity Score, FSS) and the walking performance outcome measures; 10mWT and 6MWT.

We hypothesized that there is no effect of time of day on walking. A high test-retest reliability (ICC > 0.7) is hypothesized for gait kinematics and the 10mWT. And, the third hypothesis is that there is no significant correlation between perceived fatigue and walking performances.

Methodology:

In this secondary data study, within day differences of gait tested between morning (AM) and afternoon (PM) were analysed using paired t-test and Wilcoxon Signed Rank test; while test-retest reliability of the outcome measures assessed for between-day repeatability was evaluated using Intraclass Correlation Coefficient (ICC). The correlation between fatigue score and the walking measures were tested with Pearson Correlation Coefficient.

Results:

There is no difference in gait kinematics and walking performance assessed in AM and PM sessions. We found moderate to good reliability of gait kinematics and 10mWT as indicated by the ICC. Lastly, there is no statistically significant correlation between self-reported fatigue and measures of walking capacity.

Conclusion:

Based on the results, this study suggests that pwMS do not necessarily walk differently in the afternoons compared to mornings. The retest reliability offered fulfilment in knowledge gap regarding between-day reliability testing. Self-reports of fatigue are less likely to associate with objective walking ability suggesting that there may be other influences to walking performance in pwMS, and this requires further research.

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Word count: 11 212 words

Acronyms and Abbreviations

MS	Multiple sclerosis
CNS	Central nervous system
PwMS	Persons with multiple sclerosis
3D	3-dimensional
10mWT	10-meter walk test
6MWT	6 minute walk test
QOL	Quality of life
EDSS	Expanded Disability Status Scale
FS	Functional score
ADL	Activities of daily living
ICF	International Classification of Functioning, Disability and Health
NICE	National Institute for Health and Care Excellence
FSS	Fatigue Severity Scale
HCPs	Health care professionals
QMU	Queen Margaret University
NHS	National Health Services
AM	morning
PM	afternoon
ROM	range of motion
PF	plantarflexion
lhiprom	left hip range of motion
rhiprom	right hip range of motion
lmaxpf	left maximum plantarflexion
rmaxpf	right maximum plantarflexion
ICC	Intraclass Correlation Coefficient

SEM	Standard Error of Measurement
MDC	Minimal Detectable Change
SD	Standard deviation
Sig.	Significance probability

.

Units of Measurements

°	degree of movement
m/s	meter per second
s	seconds
m	meter

1.0 Introduction

Multiple Sclerosis (MS) is an autoimmune-mediated neurodegenerative disorder of the central nervous system (CNS). One in every six hundred people in the United Kingdom has MS. This is as estimated by the country's MS Society (2016) that provides advice, education and care for persons with MS (pwMS). The malfunction of immune system in MS destroys the protective lining of nerves called the myelin, and the axons of the brain and spinal cord. This degeneration, damage and inflammation of the myelin sheath is known as demyelination. Lesions or plaques form where the myelin is attacked and in most cases the nerve fibres are severed. These then causes the smooth transmission of message signals along axons between the brain and body to be blocked or slowed down (NHS 2016).

In human physiology, communication between the brain and the rest of the body is based on the proper functioning of the body's sensory and motor capabilities. With MS, sensory and motor functions are impaired and disability sets in. This is relatable with Compston and Coles (2008) who stated that pathological changes caused become progressive accumulation of disability in pwMS. The disease besides being associated with a wide range of disability symptoms, is further characterized by exacerbations and remissions in MS (Hadjimichael et al. 2008). The vagueness of symptoms and daily fluctuations faced results in pwMS having to cope with the varied experiences and challenges of impairments of the disease.

One highly rated challenge coping with the disease expressed not only by pwMS but clinicians inclusive, is difficulty walking due to feeling fatigue. Assessing walking impairment in pwMS is common, and there already exists a considerable amount of studies on this focus (Motl et al. 2012; Noguiera et al. 2016). However, these MS studies, without exempt, comments on the lack of clear definition of fatigue and the insufficiency of understanding how pwMS may experience change in physical partaking throughout a day (Rudroff et al.

2018; Dalgas et al. 2018). It is also uncertain from studies if fatigue is significantly related to walking capacity. Considering the notably large number of MS persons worldwide, research aimed at understanding the influences of time of day and fatigue relationship to walking may facilitate development of awareness in rehabilitation and care management.

On another note, a number of outcome measures exists; for instance, the 3-dimensional (3D) gait kinematics analysis, 10-meter walk test (10mWT) and 6 minute walk test (6MWT) frequently used to measure walking in neurological conditions. These outcome measures need to be reliable, in addition to being valid, to express consistency and credibility when used as a clinical outcome. Test-retest reliability is one simple way of testing for stability and reliability of an outcome measure tested over time. There are evidences in literature of retest reliability studies to support the psychometric characteristics of the 10mWT outcome measure in populations like spinal cord injury and traumatic brain injury (Scivoletto et al. 2011; Hirsch et al. 2014), but not for MS specific population. Another drawback also is that these reliability testings' have only been established for within-day or one-week retest period. Moreover, there are no studies reporting for the 3D gait analysis outcome in pwMS (Andreapoulou et al. 2018). These limitations indicate that reliability studies are rare and further studies need to evaluate gait outcome measures statistically specific to pwMS.

This study aimed to contribute to understanding the differences in walking kinematics and performance in relation to time of day and to identify the correlation of walking performances with perceived fatigue in pwMS. This study also aimed to add to the few available studies on test-retest of the 3D gait analysis and 10mWT outcome measures of gait involving the MS population. It is hoped that with this understanding, clinicians, carers and individuals with MS can act towards management of ambulatory improvements and develop person-centred care approaches while not being weighed down by perceived fatigue. This is because walking rehabilitation has always been inhibited by concerns of fatigue and the effect of MS on gait.

With this study, an evidence-based approach to facilitating rehabilitation for pwMS may be furthered.

2.0 Literature review

2.1 Overview of MS

Nervous system is the basis by which many body mechanisms are controlled. The nervous system is made up of the CNS and the peripheral nervous system. The CNS makes up the nerves of the brain and spinal cord. As informed above, these nerve cell fibres are protected by myelin sheaths that help ensure a smooth and hastened relay of messages between the brain and rest of the body. In MS, the myelin is mistaken as foreign body and is attacked by the immune system, causing partial or complete disruption to the function of nerve fibres. It is learnt that multiple areas of scarring form at these damaged areas, and hence the name multiple sclerosis originated (National MS Society 2018). The affected neural pathways in pwMS causes a range of physical and mental functioning difficulties; influencing one's ability to perform meaningful work.

MS in general is a common disabling neurological condition affecting young adults, and hence, causing a high social burden. It is a lifelong chronic disease of unknown etiology, with four main clinical phenotypes: clinically isolated syndrome (CIS), characterised by first signs of inflammation and demyelination in the CNS; primary-progressive MS (PPMS), wherein neurological decline is observed from onset; secondary-progressive MS (SPMS), which exhibits greater neurological dysfunction with less or even no relapses, and relapsing-remitting MS (RRMS), characterised by worsening degeneration and episodes of remission (Multiple Sclerosis Trust 2017, National MS Society 2018). Figure 1 shows an overview of the typical disease progresses in MS (Miller 2004). The typical patterns or characteristics describe the different courses of the disease and affects pwMS in different ways.

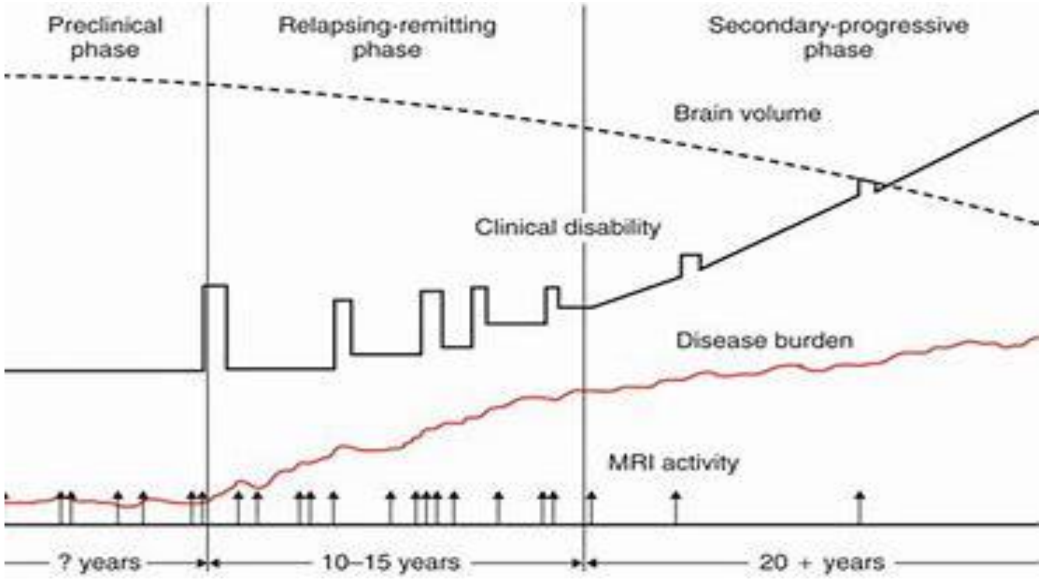


Figure 1 Overview of the typical disease progresses in MS (Miller 2004)

An estimated 2.5 million people in the world have MS (Multiple Sclerosis Trust 2017). The onset of MS can develop in individuals as young as 2 years old with almost 70% of patients manifest symptoms between ages 20 and 40 (National MS Society 2018). Statistics and registers inform that there is a clear gender differences; with women being more frequently affected than men at a ratio of up to 4:1. Largely, the occurrence of MS increases further north or south from the equator but ethnicity may differ this prevalence. Certain ethnic groups as the Australian Aborigines and New Zealanders have a markedly lower prevalence of developing MS. Scotland, especially northern east of Scotland and Canada has particularly high number of MS persons.

There is no cure yet for MS. The life expectancy for pwMS is averaged 7 years lower than the general population (Multiple Sclerosis Trust 2017). Nevertheless, this gap appears to be getting smaller and quality of life (QOL) of pwMS are being enhanced with improved treatment. MS can be a challenging condition to live with as pwMS exhibit a wide variety of symptoms from the random distribution of the demyelination lesions in the CNS. Lately, these symptoms are better managed not only at individual level, but also clinically and at rehabilitation level. The emphasis in managing MS patients has evidently shifted to multi-disciplinary teams, with which increased MS based research are crucial for decision making in this population.

2.2 Defining disability measures in MS

The Expanded Disability Status Scale (EDSS) is a classification scale widely used in assessment of level of MS disability. In clinical context, the EDSS is used to monitor progression or changes in the level of disability in pwMS. John Kurtzke in 1983 founded this scale which ranged from scoring stages of 0.0-10.0. It is based on a half-point unit increment with higher scores representing greater disability (Kurtzke 1983). EDSS of 1.0-4.5 are defined by pwMS who are fully independent ambulators; and each precise decimal scoring unit is demarcated by Functional Score (FS). The FS is formed of measures of eight functional systems including sensory, visual and bowel and bladder function. Grades 5.0 and above represent more severe disability with obvious walking difficulties impairing activities of daily living (ADL). A representation of the EDSS features is presented in Figure 2 (Multiple Sclerosis Trust 2018). The EDSS, although has its flaws as it is denominated by walking or mobility and does not capture the impact of MS on individual's functioning in society, it is nevertheless recognized as the 'gold standard' or as a primary outcome measure in classifying disability.

In relation to understanding MS and limitations to social participation, the World Health Assembly in 2001 commended and sanctioned the International Classification of Functioning, Disability and Health (ICF) framework in providing a basis for defining health and disability (WHO 2018). The framework recognizes that health conditions and their effects are altogether the integration of social and medical well-being. According to the ICF framework, co-interaction between health, personal and environmental factors are the principals of individual functioning (WHO 2018). Activity and participation describes an individual's functional status and involvement ability which includes taking part in commitments, work or social interests. The MS disease which is known to impair body function usually results in activity limitation in pwMS, as such described by ICF, affects participation willingness.

The ICF is suggested to be applied as an international reference in all aspects of health; be it education, providing support services and in clinical practice. The NICE (2014) guidelines state that rehabilitation should aim towards promoting self-management and enhance functional independence of patients through patient education. Physiotherapy in MS rehabilitation are primarily focused on improving mobility problems and fatigue symptoms of pwMS by means of exercise provision. Gaining participation for exercise is possibly easier when clinicians and pwMS understand the extent of how much fatigue and exercise involvement interact in influencing positive exercise experiences. Therefore, research in understanding fatigue and gait changes in relation to disability may be of value in maximizing potential for rehabilitation care as in this study.

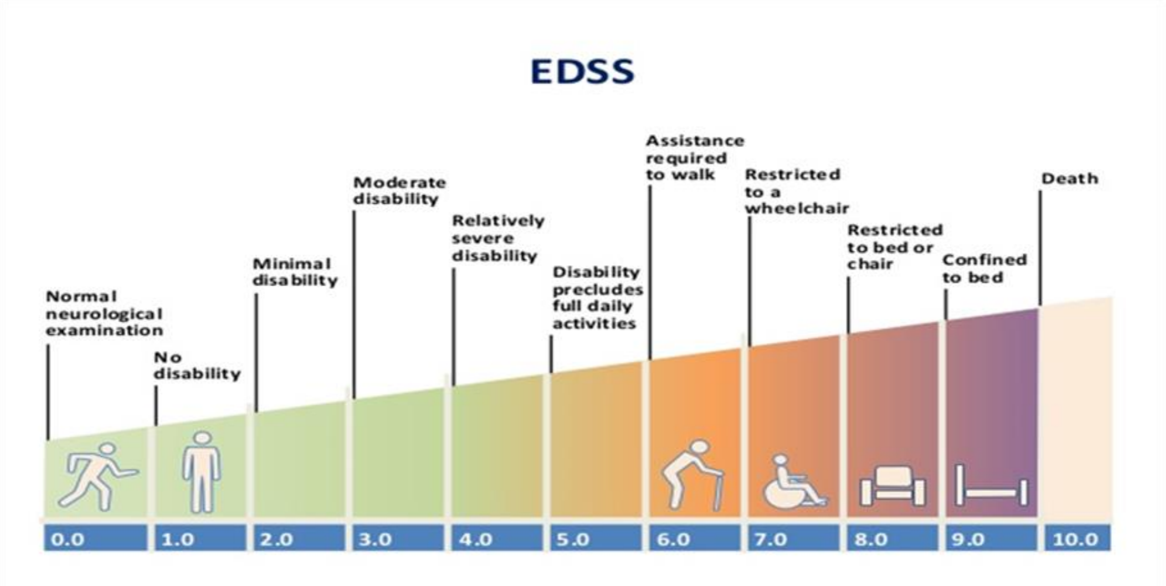


Figure 2 Expanded Disability Status Scale (EDSS) (Multiple Sclerosis Trust 2018)

2.3 Fatigue symptom in pwMS

Reporting statistics reveal that an average of 50% of pwMS require walking aid and another 10% become wheelchair dependent following a 15-year MS diagnosis period (Kelleher et al. 2010). Inopportunely, about 85% of the MS population struggle with gait disturbances in the early course of their disease (Bethoux and Bennett 2011). It is most likely also that falls in MS are results of postural instability, gait irregularities and muscle weakness which are attributable to fatigue. In fact, study results reported that there is significant effect of MS fatigue symptom on gait with more than 50% experiencing falls following compromised walking ability (Remelius et al. 2012). In relation to this, McLoughlin et al. (2016) adds that symptoms of weakness and fatigue commonly alter the normal walking mechanics in pwMS. A possible rationale to this may be that alterations in normal walking pattern increases cost of energy expenditure required to perform walking, which then seemingly introduces fatigue.

PwMS commonly describe fatigue as a constant sense of weakness causing tiredness which is exacerbated usually with activity and as the day progresses (Kayes et al. 2011). Fatigue as defined by Kos et al. (2008) is the lack of energy to partake in ADL which can be physically or mentally demanding. With scientific explanation set aside, pwMS equated feeling fatigue to factors such as personal experiences that are closely related to aspects of their lives. This includes employment, relationships, expectations and ability to follow health-related recommendations (Smith et al. 2013). MS-related fatigue to date has little scientific explanation and is difficult to describe nor measure. It takes on the nature of MS by being unpredictable and individual to each person. Still studies are required to deliver knowledge, establish facts and reach new conclusions about MS-related fatigue.

"'Really heavy.... I feel as though I have got concrete blocks. That is how I feel all the time'. (Donna, Age 52, Relapsing remitting MS)"

"'No, my legs were also not picking up properly, so if I couldn't walk safely there was no point'. (Julie, Age 52, Relapsing remitting MS)"

These expressions of fatigue and fear of falling are as quoted from an interpretive descriptive study reported by Kayes et al. (2011, page 633 and 634). The study aimed at exploring barriers to ADL participation from the perspectives of pwMS. Only 10 participants were involved in this study, but the focused sample selection method provided the study findings with information from participants of diversified encounters coping with MS disease. This further fulfilled the saturation point criterion of a qualitative study; as enough data was gathered and the reported themes answered the proposed research question. Also, it is unclear what the definition of physical activity was in their study, but participants were pre-informed of this to attain the phenomenon of interest. This impedes the understanding of the expanse of physical activity causing expressions of fatigue amongst the participating pwMS. Nevertheless, these reported expressions are representative of real life descriptions of how fatigue affects pwMS in terms of physical participation; from which meaningful conclusions can be communicated.

With regards to physical participation, it cannot be denied that walking constitutes as the biggest part and is an important complement for daily living. In other words, walking is the main means of locomotion. Unfortunately, pwMS might find themselves troubled by fatigue which causes difficulties in walking. This indeed may be one of the first symptoms to be noticed in MS (MS Society 2016). PwMS then may start to refrain from undertaking an activity or from going out for fear of feeling too tired and not able to complete the amount of walking required to fulfil any task. As noted, reasonable amount of studies has been done to investigate the effects of this fatigue symptom in MS and to consider the likely detrimental consequences to walking. These studies reported evident alterations in gait, but the extent to which fatigue impose on the gait variations however, are vaguely known.

2.4 MS-related fatigue and its association to walking

Fatigue and gait impairments are two of the most disabling and recurring symptoms in pwMS. Walking in pwMS is not solely limited by impairments but also by factors as fatigue, and so, assessments of gait can be complex. Fatigue is deemed to be multi-factorial and it is difficult to ascertain the real cause in order to overcome this symptom. For example, the widespread of axon demyelination is usually said to cause fatigue (Steens et al. 2012). Likewise, MS related conditions as infection, lack of sleep, pain, and illness can indirectly cause fatigue (Andreasen et al. 2011). With the absence of cure for MS, management of fatigue symptom is necessary to reduce impact on the person’s lifestyle. The cause of MS fatigue, its clinical characteristics, and its relationship to other symptoms, notably gait difficulties remain poorly understood based on literature.

There are studies assessing fatigue in MS that found self-reports of fatigue as having positive correlation with changes in gait kinematics (Huisinga et al. 2011; Motl et al. 2012). In the study of Motl et al. (2012), 44 persons with mild MS completed walking and fatigue measures. Findings of their study suggests that gait speed and stride length were significantly and inversely associated with energy cost of walking, and that the elevated cost of energy in walking is positively associated (p=0.31) with fatigue. Similarly, Huisinga et al. (2011) in their study evaluating relationship between fatigue and gait alteration, supported the expectation that fatigue is directly proportional to the use of energy in walking. These cross-sectional studies however are limited in generalizability as different levels of MS disability were not represented and the initial contribution of gait deficit was not accounted for.

Also, McLoughlin et al. (2016) in their study aimed at analysing induced fatigue in pwMS to changes in gait parameters, found gait specific deficiencies of reduced ankle dorsiflexion at initial contact phase and increased power use at hip and knee joints. This resulted in feeling of exertion, followed with greater self-reports of fatigue. The study had 10 healthy persons as comparison, however they did not complement the larger sample size of 34 MS participants. Furthermore, the 6MWT was done using a shorter pathway that required larger degree of turns instead of the 90° standard test protocol, which may have caused increased fatiguability.

As a whole, these studies from Huisinga et al. (2011), Motl et al. (2012) and McLoughlin et al. (2016) report that there are significant associations between gait and fatigue, and these findings are independent to disability status. It is however recognised that self-reported fatigue questionnaires used in such studies posed as limitation to these studies. Therefore, this study anticipated that it is ideal to quantify gait outcome measures over time to show true reliability or consistency of measures.

2.5 Defining fatigue through rehabilitation

In rehabilitation, fatigue is seen as a barrier to prescribing exercises and in attaining patients' participation. Studies have assessed for the relationship between improvements of fatigue with improvements of walking through rehabilitation. For instance, Sacco et al. (2011) in their study had a small sample size of 24 MS participants and 19 healthy control participants to analyse gait changes and correlation with fatigue. It was found that gait parameters were correlated with fatigue physical score, and improvements in gait parameters were correlated with improvement of fatigue. Participants in this study completed 3 weeks of individualised multidisciplinary rehabilitation interventions which included aerobics, endurance exercises, water or hippo therapy and ADL retraining. These form of rehabilitation exercises however was not focussed solely on gait retraining and may have overall influence to the reported findings on gait and fatigue improvements.

Similarly, a systematic review aimed to summarize the effect of exercise on self-reported fatigue in MS patients discovered that the likelihood of exercise in reducing MS fatigue is positive (Andreasen et al. 2011). Among limitations to note here are the low sample sizes and that the reviewed studies measured fatigue as a secondary measure. These may have resulted in low statistical power and reduced the likelihood that the results reflected true effect. Other supporting evidences and review studies have shown positive effects of exercise and rehabilitation on fatigue symptoms (Dalgas et al. 2007), QOL (Motl and Gosney 2008) and muscle strength (Kjolhede et al. 2012). Khan et al. (2011) as well evaluated from published systematic reviews the benefits of rehabilitation; that of which included improvement in physical function and participation in pwMS.

There is likewise sufficient evidence on the range of rehabilitative treatments available in support of MS symptoms improvement (Dalgas et al. 2007; Rampello et al. 2007). However, there is an underrepresentation in the literature of fatigue perception and its effect on walking participation. Fatigue is not objectively measurable and deters the purpose of estimating for improvements or declines in rehabilitation. This implies that there is a break in understanding the optimal frequency, intensity, and the cost-effective form of rehabilitation for mobility problems in pwMS. Also, with fatigue being a difficult construct to measure, the characteristics of fatigue is questionable and there can be varied unexplainable reasons for this symptom in MS.

2.6 Effect of time of day on walking

It is well reported by pwMS that fatigue levels worsen as time of day progresses. While it is expected that fatigue levels affect physical functioning and mobility, the effect of time of day on gait variability and impact on walking has been studied to better interpret for important changes. Study findings in general display conclusions that can be contentious to what is assumed of pwMS in relation to poorer performance within the day. For instance, Feys et al. (2014) assessed for within-day variability in walking in pwMS to identify effects of disability and test method (short and long walking tests) on this variation. They found greater changes in ambulatory function with short compared to long walking tests when assessed for within-day variability. They also found that the differences are independent to the MS disability when measured at induced fatigue. The results suggest that with habitual walking characteristics (long-distance and normal paced), variations in walking from morning to afternoon in pwMS are not significantly different.

In another study examining gait and fatigue changes from morning to afternoon in a single day, self-rated fatigue increased significantly while gait parameters remained constant (Morris et al. 2002). The study specified morning and afternoon measurement times to be 5 hours apart; and the foot switches of the stride analyser used to analyse gait were not removed between trials. The study hereby characteristically attempted to decrease variances in measures to reduce error and increase power of the study. Also, missing data were addressed, hence there is confidence in drawing inference based from this study. The study although relevant to what is believed among pwMS, but the findings are only applicable to pwMS with mild to moderate EDSS disability scores. It also reckons that ambulation and feeling of fatigue are separate factors, and that objective measures in addition to self-reports of fatigue is desirable when considering for changes in pwMS.

2.7 Quantifying fatigue using Fatigue Severity Scale

Despite the impression of decreasing energy level as the day progresses, fatigue is by far measured only subjectively via self-reports. There are several self-reporting fatigue outcome measures like the Fatigue Severity Scale (FSS) (Krupp et al. 1989) and Fatigue Impact Scale (Fisk et al. 1994) available. These outcomes have been researched in populations of MS and have adequate reliability and validity properties as reported in studies (Amtmann et al. 2012; Ottonello et al. 2016). The 9-item FSS questionnaire is popularly used and is applicable for measuring MS fatigue ranging from physical to mental aspects of daily living. Learmonth et al. (2013) carried out a six-month long study period involving 86 MS participants to determine the psychometric properties of the FSS. The findings revealed good test-retest reliability of the FSS with ICC of 0.75. Other published studies, although not individual to the MS population; report FSS having ICC of 0.88 (Valko et al. 2008) and 0.93 (Whitehead 2009). Thus, the FSS is considered a reliable measure for evaluation of fatigue perception as used in this study.

On the other hand, a known limitation to the FSS being a self-reported assessment is that the responses can be subjective or have social desirable impact. The lack of objective measures to quantify perceived fatigue clearly warrants future exploration. Several qualitative studies have been carried out reporting experiences of pwMS in hope to better understand feelings of fatigue and the effect towards involvement in ADL. Being reliant only on such subjective assessments do not provide for in-depth comprehension of limits of fatigue affecting physical role. Majority of MS participants from a study by Kayes et al. (2011) that completed a semi-structured interview; concluded that they wished they were better informed about the effects and results from being involved in physical activity. They also expressed the view that such information, particularly if it came from a credible professional, would impart understanding of the related symptoms they are experiencing and make them less anxious when getting involved in rehabilitation. It seems that these messages or advice are rare in healthcare provision, probably due to the lack of objectivity in assessing the significance of fatigue.

In a study involving healthcare professionals' (HCPs) perceptions of challenges and barriers of MS fatigue management, fatigue was regarded as a 'professional challenge' and 'stirring conflict' among the interdisciplinary team (Smith et al. 2013). Again, pwMS in this study also described disappointment that HCPs exercise prescriptions to them did not match their perception or experience of fatigue. Smith et al. (2013) reported that pwMS commonly were frustrated that HCPs had difficulties suggesting exercises and advising of their exercise limits. In such instances, a more consistent understanding of fatigue experiences and the perceptions of pwMS towards physical activity engagement is necessary. This may then facilitate better and encouraging exercise experiences for pwMS, improve HCPs choice of exercise recommendations to pwMS, as well as sustain confident monitoring of exercise progression in rehabilitation.

2.8 Assessment of walking

Gait and walking are terms mostly used interchangeably with no clear distinction in literature between these two terms. The primary concept is in the energy used for progression in motion. Assessment of gait is normally directed towards identifying any faults or impairments in walking. Walking impairment may be life changing and is commonly monitored as an indicator of progression of disease and disability. There are various clinical outcome measures designed to address walking ability. One of the recommended standardized gait assessment is the 3D gait analysis. It is referred to as the benchmark criterion for gait assessment to the point of identifying underlying mechanics of gait deterioration or alterations (Cameron and Wagner 2011). The psychometric properties of the 3D gait analysis although have not been reported specifically for the MS population, accounts for high inter- and intra-session reliabilities (Andreopoulou et al. 2017). Besides the 3D gait analysis, walking ability typically is measured in clinical MS management with outcome measures such as the 10mWT and the 6MWT.

The interpretation of changes in gait and walking capacity through objective outcome measures requires the knowledge of reliability, validity and responsiveness of the measure. The study by Andreopoulou et al. (2017), performed a principal search updated as of May 2017, to evaluate the psychometric properties of walking outcome measures used for assessing walking performance and walking effort in pwMS following use of assistive walking technology. Their review identified that there is no evidence available on the psychometric properties of 3D gait analysis measured in MS. As for studies assessing the 10mWT, evaluation of methodological quality revealed fairly good quality of evidences for test-retest reliability. While researchers mostly have demonstrated within-day reliability of the 10mWT, there are almost no studies that have determined the between-day reliability testing of the 10mWT and especially in pwMS. The within-day reliability testing alone is considered not adequate knowing that pwMS may experience day-to-day fluctuations in performance.

Corresponding to the above, Nilsagard et al. (2007) in their study performed test-retest of the 10mWT assessed on three trial measures involving same day testing and at 1 week apart. 43 participants were tested and resulted in high ICC with same day testing (ICC=0.92) and between-day testing (ICC=0.99). Interestingly, the same high reproducibility of ICC (0.97) was reported in Morris et al. (2002) with same day repeated testing of the 10mWT. This demonstrates that both within- and between-day variability is established with regards to test-retest reliability. Caution must however be taken when interpreting these studies as there are limitations of small sample size, the varied disability levels of MS and the unavailability of study with longer interim periods that may alter clinical relevance of the findings. Considering the complexity of walking task, research on reliability of gait outcome measures like the 10mWT must be continuously evaluated to justify for its use as a trustworthy clinical assessment tool.

2.9 Rationale for this study

PwMS tend to curb their activities because of fatigue and walking limitations. Besides, walking impairments added on with the uncertainty of MS symptoms can be equally disabling. It remains a query on whether fatigue is just a matter of self-perceived factor rather than caused by increased activity. A number of research have considered assessing gait outcome measures at several different times of a day to identify for declining changes in walking characteristics and performance in pwMS (Fry and Pfalzer 2006; McLoughlin et al. 2016). More recent studies have featured the use of 3D gait analysis which benefited from the perspective of obtaining detailed analysis of changes in gait for pwMS (Huisinga et al. 2011; Lizama et al. 2016). However, regardless of these available studies, limited considerations are directed towards time of day effect on alterations in walking in pwMS. Thus, the variability in gait with time of day; differentiating morning and afternoon ambulatory performance is regarded a purpose for analysis in this study.

Additionally, with fatigue reported as a barrier to physical participation (Borkoles et al. 2009; Stroud et al. 2009) and little known about the day-to-day changes for pwMS experiencing this symptom, other means of attaining objectivity in researching this challenge is demanded. A suggested approach is to analyse for test-retest reliability so that consistency of the findings of outcome measures measured over time is attained. Outcome measures like the 10mWT and 6MWT are commonly described in studies, but usually concentrated on single day repeated reliability measures. Unlike other outcome measures for gait assessment, it is evident also that research has not studied the reliability, validity and responsiveness of 3D gait analysis amongst pwMS. Without good between-day retest reliability, it is difficult to conclude that the measures are accurate representation of performance in pwMS; besides assuming for influences such as environmental, psychological or even related to limitations of the testing methodological processes.

By way of explanation, it will be advantageous to know whether time of day when outcomes of fatigue and gait are being measured or reported, matters. Nonetheless, due to the poorly understood multi-factorial nature of fatigue and the unpredictable MS-related functional changes, it will also be useful to measure for the test-retest reliability of walking in pwMS. Walking ability measured at the same time of day for a few trials over a couple of days would serve this purpose; incorporating between day test-retest analysis. This study proceeds with the opportunity to analyse the between-day test-retest reliability of the primary results from the 3D gait analysis and the 10mWT performance outcome measure. This provides for understanding the true retest reliability of these measured outcomes.

Thirdly, the unspecified effect of feeling fatigued to possible changes in walking capacity in pwMS, is a problem which is accentuated when relating particularly at rehabilitation facilitation. A question of if this pronounced symptom of fatigue has effect in MS and how it may associate to walking is raised amongst pwMS, carers and clinicians. In literature, prominent studies typically report fatigue using self-assessed questionnaires and are assessed along with gait measures. These self-reports of fatigue are however said to be limited when implementing for rehabilitation appropriateness as they are subjective in nature and may not propose beneficial findings. As studied by Vucic et al. (2010), answers to these questionnaires may be influenced by the respondents' physical, mental and emotional well-being at that time of reporting. This results in fatigue being a qualitative value and not objectively understood.

In monitoring for changes in fatigue levels and walking ability, quite a large part of MS research has been dedicated to studying the relationship between fatigue and walking (Huisinga et al. 2011; Dalgas et al. 2018). It is interesting that studies found conclusions that are varied with respect to the attribute of fatigue outcome measure used. These findings found that reports of fatigue assessing physical or mental effort were only weakly correlated to walking capacity, while greater significant correlations were found for fatigue scores assessing general health perceptions with response to walking performance. There is still an obvious gap in literature regarding the inferences of relationship between fatigue and gait; and their usefulness when evaluating pwMS. Therefore, the analysis of correlation between FSS and walking performance of pwMS in this study would add to the knowledge of ascertaining for any such purposeful relationship.

On the whole, in line with advancement in research and evidence-based practice, this secondary study was conducted to establish effects of time of day on functional walking in pwMS and to determine the between-day test-retest reliability of walking, given the 3D gait analysis and 10mWT data presented in the primary study. This study also reasoned the relationship between walking performance and perceived fatigue in pwMS. Understanding walking variability, knowledge of reliability in measures and recognising the relationship of fatigue limiting participation may well inform research towards maximizing rehabilitation potential. Such informed research may arguably result in longstanding adherence and improved willingness to perform physical activity then is currently seen lacking among pwMS. With better adherence and participation, significant improvements in physical, mental and social wellbeing is anticipated for pwMS. This study may also facilitate improvement of rehabilitation strategy planning, add to the evidence on mobility specific interventions and enable development of larger longitudinal studies as such in the MS population.

3.0 Aims and Hypotheses

This secondary data study analysis was done following a primary study by Scott et al. (2013). The primary study investigated the effect of Functional Electrical Stimulation on walking and incorporated the use of walking-based outcome measures assessed on multiple testing occasions. The outcome measures used were the 3D gait analysis, 10mWT and

6MWT; in addition to reports of fatigue using the FSS. The primary data on repeated assessments of these gait outcome measures and fatigue assessment informs for the intentions of this secondary study.

The aims of this current study are:

1) to determine if there is statistically significant difference between gait kinematics (3D gait analysis) and walking performance (10mWT and 6MWT) as assessed in the AM and those assessed in the PM
2) to determine the between day test-retest reliability of the assessment of gait kinematics and walking performance assessed at the same time of different days
3) to assess the correlation between fatigue scoring (FSS) and the walking performance tests

The null and research hypothesis for statistical testing are: 1) there is no significant differences between the AM and PM assessments of gait kinematics and the 10mWT and 6MWT walking performance tests (i.e. no effect of time of day on walking in pwMS), 2) there is a high test-retest reliability (ICC of 0.7 or more) for gait kinematics and the outcomes of 10mWT when assessed on the same time of the day (AM or PM) over a period of 3-14 days apart, and 3) there is no statistically significant correlation between the FSS, 10mWT and the 6MWT accordingly.

4.0 Methodology

4.1 Methodology of primary study

The primary study design was a counterbalanced, within-participant, and a repeated measure layout with data collected through laboratory assessments at Queen Margaret University (QMU), Edinburgh. In the primary study, MS participants diagnosed by a neurologist, geriatrician, or rehabilitation specialist and fulfilled the inclusion exclusion criteria were recruited via a National Health Service (NHS) community physiotherapy service in Edinburgh.

The inclusion criteria were those from the age of 18 to 70 years old and referred for physiotherapy management. Able to ambulate at least 15 meters on repeated measures with or without walking aid was another criterion of inclusion. Exclusion criteria included those unable to ambulate the minimal 15-meter required distance, those with visual or neurological impairment, those who are pregnant and breast feeding, and those with a recent exacerbation or relapse of MS in the past 30 days.

Participants completed the FSS fatigue questionnaire, the 3D gait analysis and the timed walking tests at different times of the day over 4 separate visits. The time frame between the repeated assessments ranged between 3 days to 2 weeks; a reasonable compromise between recollection bias and unwanted clinical change in the participants. The gait outcome measures were completed twice for each AM and PM measurements and the time of day assessment was counterbalanced per visit. Morning (AM) session ran between 09:30-11:00 and the afternoon (PM) session was between 13:00-14:30.

Participants first performed the 3D gait analysis which was recorded using the Vicon 3D motion analysis system (Vicon Motion Systems, Oxford, UK). A pathway of 7-meter in length was walked barefoot and participants completed the same length each for three tested gait parameters. The gait parameters were hip range of motion (ROM); left and right, maximum ankle plantarflexion (PF) angle; left and right, and stride length during swing phase as derived from the 3D gait analysis. Rest was allowed between trials if required.

Following the 3D gait analysis, participants completed two trials of the 10mWT and one trial of the 6MWT. Participants were timed and instructed to walk a 10-meter measured walkway at their preferred pace (Rossier and Wade 2001). As for the 6MWT, participants were asked to walk as far as possible within a marked out 16.5-meter elliptical course (Enright 2003). The same preferred pace of walking was encouraged and total distance walked in 6 minutes was measured. Assistive devices if used were kept consistent and documented from test to test.

4.2 Methodology of current study

The following methodology was applied to articulate this current study's rationales and aims.

i) Data collection

Anonymized data from the primary completed study in 2013 was obtained from supervisor. These data included de-identified FSS score, the 3D gait analysis measurement and the 10mWT and 6MWT outcome measure recordings. These were extracted using protected databases on a secured network server. The anonymity of data was ensured throughout this process by restricting data movement only between supervisor and researcher.

ii) Data analysis

Descriptive characteristics of participants were established. For statistical presentation and best estimation, the average of each two AM and PM measurements were calculated. Assessment of normality was tested via Shapiro-Wilks statistical test as the study involved a small sample size.

Following the assumption of normality, the effect of time of day (AM vs. PM) was evaluated using paired t-test for parametric and a Wilcoxon's test for non-parametric data obtained.

The test-retest reliability of gait outcome measures was assessed using Intraclass Correlation Coefficient (ICC (2,1)) and reported based on 95% Confidence Interval (CI). Categories used for interpreting ICC are as suggested by Portney & Watkins (2000); ICC values of >0.75 represent good reliability, 0.50 – 0.75 represent moderate reliability, and ICC values of <0.50 represent poor reliability. To further support findings of test-retest reliability, Standard Error of Measurement (SEM) and Minimal Detectable Change (MDC) statistical calculations were carried out.

A Pearson Correlation Coefficient was calculated to assess the strength and relationship between the FSS, 10mWT and 6MWT. The rule of thumb for interpreting the size of correlation coefficient is as cited by Hinkle et al. (2003). The interpretations are; 0.9-1.0 = very high correlation, 0.7-0.9 = high correlation, 0.5-0.7 = moderate correlation, 0.3-0.5 = low correlation and 0.0-0.3 = no to little correlation, if any.

Statistical significance was accepted at p<0.05 for hypothesis testing analyses. All statistical tests were carried out using IBM SPSS Statistics version 23 and missing values in the data range were excluded.

iii) Ethical considerations

Apart from the original approval obtained in the primary study, this study was reviewed and approved by QMU Divisional Ethics panel.

Anonymity of the extracted data in this secondary analysis was maintained using participant codes. No data leak was ensured during access and viewing of these data by avoiding scan or email of original documentations. Anonymous data collection forms were accessed in hard copy obtained from supervisor and data extraction was done via databases that directly stored data to the university's system server. Final data was stored systematically and password secured on QMU's protected network.

5.0 Results

5.1 Demographic characteristics of the participants

Demographic characteristics are reported based on the demographics of participants in the primary study. The stated results are given with reference to availability of data at each AM and PM session as well as at each assessment day. Although the primary obtained data consisted of a greater number of respondents, but for the purpose of this study, only the data of 12 participants who completed all the study assessments or fulfilled at least one AM and one PM assessment was selected for analysis. The participant characteristics are provided in Table 1. There were 3 females and 9 male participants with the total mean age of 47.8 years old. EDSS score of the participants were between 2.0 and 4.0; representing pwMS of minimal to significant disability but self-sufficient in completing walking with some rest.

Table 1 Participant characteristics

Characteristics	
Gender, n	
Male	9
Female	3
Age, years	
Mean age	47.8
S.D.	6.6
BMI, kg/m²	
Mean	28.3
SD	3.9
Walking stick users, n	4

SD = Standard deviation

Table 2 Normality statistics for 3D gait analysis, 10mWT and 6MWT

			z-value	Shapiro-Wilk (Sig.)
lhiprom (°)				
AM	Skewness	-0.469	-0.736	0.606
	Kurtosis	-0.400	0.325	
PM	Skewness	-0.165	-0.259	0.992
	Kurtosis	0.789	0.640	
rhiprom (°)				
AM	Skewness	0.214	0.336	0.118
	Kurtosis	-1.634	-1.326	
PM	Skewness	-0.153	-0.240	0.838
	Kurtosis	-0.842	-0.683	
lmaxpf (°)				
AM	Skewness	0.198	0.311	0.156
	Kurtosis	2.367	1.921	
PM	Skewness	1.514	2.377	0.017
	Kurtosis	1.917	1.556	
rmaxpf (°)				
AM	Skewness	0.190	0.300	0.994
	Kurtosis	0.239	0.194	
PM	Skewness	0.439	0.689	0.724
	Kurtosis	0.171	0.139	
Speed (m/s)				
AM	Skewness	0.127	0.199	0.999
	Kurtosis	-0.506	-0.411	
PM	Skewness	0.188	0.300	0.484
	Kurtosis	-1.209	-0.981	
10mWT (s)				
AM	Skewness	0.907	1.372	0.008
	Kurtosis	-1.008	-0.788	
PM	Skewness	0.951	1.439	0.055
	Kurtosis	-0.534	-0.418	
6MWT (m)				
AM	Skewness	-0.913	-1.150	0.078
	Kurtosis	-0.964	-0.607	
PM	Skewness	-0.992	-1.250	0.236
	Kurtosis	-0.249	-0.157	

Sig. = Significance probability

5.2 Test for normality and effect of time of day (AM and PM) on walking

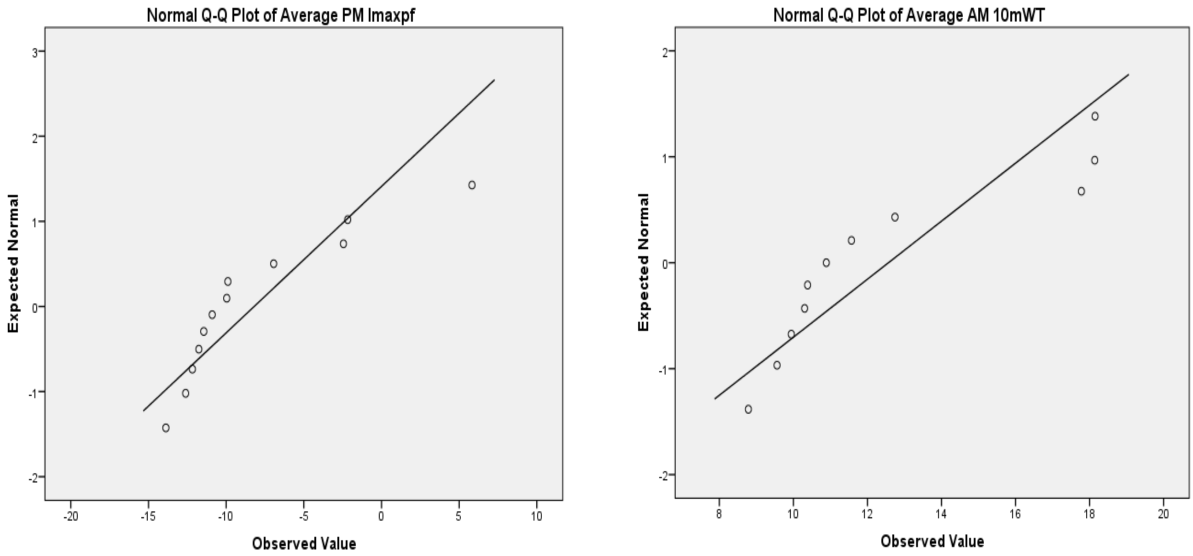
5.2.1 Normality testing

The assumption of normality was checked for outcomes of the 3D gait analysis and walking performance to determine whether the sample data has been modelled by a normal distribution. This assumption also allowed to compute for the use of the t-test statistical testing in assessing for the time of day effect on participants walking. The null hypothesis used for this normality testing is that the sample data are not significantly different than a normal population. Shapiro-Wilk's test showed that all outcomes, except the Imaxpf (PM assessment) gait parameter and the 10mWT (AM assessment), were normally distributed ($p>0.05$). The results for each outcome are presented in Table 2 (refer above).

It is suggested that another formal normality testing is by looking at skewness and kurtosis. For small samples sizes of less than 50, the null hypothesis is rejected if the absolute z-scores for either skewness or kurtosis appears greater than +1.96; with alpha level of 0.05 (Hae-Young Kim 2013). This is seen with the z-value calculated and reported for Imaxpf parameter (skewness=2.377). The 10mWT alternatively displayed z-values (skewness=1.372, kurtosis=-0.788) which are significantly different from zero; thereby interpreted the non-normal sample distribution.

In addition to that, a visual inspection of the normal Q-Q plot was done to ensure the right normality assumption (Loy et al. 2015). The probability plots for the Imaxpf parameter and the 10mWT are as presented in Figure 3. From the output, all the plotted points do not fall approximately along the normal distribution reference line, hence, normality is not assumed for the Imaxpf parameter and the 10mWT.

Figure 3 Normal Q-Q plot graphs for lmaxpf (PM) and 10mWT (AM)



5.2.2 Differences in AM and PM assessment of 3D gait analysis parameters, 10mWT and 6MWT

The effect of time of day on walking parameters and walking performance was tested by paired t-test and Wilcoxon statistical tests accordingly. Since the data for lhiprom, rhiprom, rmaxpf and speed followed a normal distribution, the appropriate parametric test for the small sample size in this study is the t-test. The lmaxpf and 10mWT data that are not normally distributed; a non-parametric Wilcoxon Signed Rank test was performed. As for the 6MWT, the data set only reported for a very small number of participants (n=7) with available paired measurements of the morning and afternoon assessments. The small sample size for the 6MWT therefore lacked in sufficient power to provide meaningful results on the distribution test and so, a non-parametric Wilcoxon test was performed to compare the repeated measurements.

Table 3 shows the results from the paired t-test analysis whilst Table 4 shows the Wilcoxon test results as the non-parametric alternative of the t-test for reporting this association. Paired sample t-test conducted for four of the five gait analysis parameters; lhiprom, rhiprom, rmaxpf and speed; found that there was no statistically significant difference between the scores for AM assessments and PM assessments (p>0.05). This means that we fail to reject the null hypothesis; that there is no effect of time of day on gait kinematics. There is thus insufficient evidence to prove that pwMS in this study walked any different in the morning as compared to in the afternoon.

Table 3 Paired t-test for 3D gait analysis

		Mean	t	Sig.	95% Confidence Interval	
					Lower	Upper
lhiprom (°)	**AM**	35.95	1.687	0.120	-0.44	3.35
	PM	34.50				
rhiprom (°)	**AM**	36.15	1.666	0.124	-0.38	2.75
	PM	35.00				
rmaxpf (°)	**AM**	-10.35*	0.355	0.729	-2.32	3.21
	PM	-10.80*				
speed (m/s)	**AM**	0.71	0.905	0.385	-0.03	0.07
	PM	0.69				

Sig. = Significance probability

*negative values represent parameters of ankle plantarflexion.

As for the non-parametric Wilcoxon tests (Table 4), the lmaxpf gait parameter (Z=-1.344, p=0.182), the 10mWT (Z=-1.956, p=0.050) and the 6MWT (Z=-1.183, p=0.237) indicated that AM measurements were not statistically significantly different from the PM measurements. Also, there were variations in number of participants with average PM measurements lesser than the average AM measurements, however, the differences in measurements were small and failed to result in statistical significance. Here again, we fail to reject the null hypothesis; by which there is no effect of time of day on walking performance. It is highly probable then that the observed average differences in measurements happened by chance.

Table 4 Wilcoxon Signed Rank test

		Mean	Rank	Z-value	Sig.
Imaxpf (°)	**AM**	-10.36*	4/12 participants with average PM<average	-1.334	0.182
	PM	-8.20*	AM		
10mWT (s)	**AM**	12.57	2/11 participants with average PM<average	-1.956	0.050
	PM	12.96	AM measurements		
6MWT (m)	**AM**	299.98	5/7 participants with average PM<average	-1.183	0.237
	PM	293.39	AM measurements		

Sig. = Significance probability
*negative values represent parameters during plantarflexion.

5.3 Test-retest reliability of the gait analysis and 10mWT

To inform for test-retest reliability of the 3D gait kinematics analysis and the 10mWT, ICC was performed and findings are detailed in Table 5.

ICC for AM sessions and PM sessions for all assessed parameters of the 3D gait analysis and outcomes varied between 0.506-0.970 indicating moderate to good reliability. The highest ICC values in both AM (ICC 0.970) and PM (ICC 0.950) assessment was reported for the 10mWT indicating the outcome measure has good reproducibility when assessed at repeated measures over the between-day test period.

For the 3D gait analysis specific; among all the other parameters, speed exhibited highest consistency (ICC 0.931-0.935).

Table 5 also included two other statistical values; the SEM and MDC which are used to estimate the standard measurement error and smallest amount of change detectable by the outcomes beyond the measurement error in the test-retest reliability analysis. SEMs are low and MDCs of <10° for gait parameters ROM and <2 seconds for the 10mWT was reported.

Table 5 ICC, MDC and SEM measures for the 3D gait analysis parameters and 10mWT

		ICC	95% Confidence Interval		SEM	MDC_{95}
			Lower	Upper		
lhiprom (°)	**AM**	0.672	-0.322	0.918	4.33	8.48
	PM	0.799	0.107	0.955	3.36	6.59
rhiprom (°)	**AM**	0.892	0.567	0.973	2.19	4.28
	PM	0.859	0.375	0.968	2.02	3.96
lmaxpf (°)	**AM**	0.687	-0.261	0.922	4.26	8.35
	PM	0.804	0.131	0.956	2.00	3.92
rmaxpf (°)	**AM**	0.506	-0.988	0.877	4.80	9.42
	PM	0.960	0.823	0.991	1.61	3.16
speed (m/s)	**AM**	0.931	0.720	0.983	0.05	0.10
	PM	0.935	0.712	0.985	0.06	0.11
10mWT (s)	**AM**	0.970	0.887	0.992	0.91	1.79
	PM	0.950	0.780	0.989	0.95	1.86

ICC = Intraclass Correlation Coefficient, SEM = Standard Error of Measurement, MDC_{95} = Minimal Detectable Change at 95% Confidence Interval

5.4 Correlation between fatigue and walking performance

The association between fatigue score and walking was assessed using the Pearson Correlation test. Table 6 presents the correlation results between the FSS, 10mWT and 6MWT.

Results indicated weak and no statistically significant correlation between FSS and 10mWT (r =0.173, p=0.610) and also between FSS and 6MWT (r =-0.138, p=0.745).

However, a statistically significant correlation ($p<0.05$) was observed between the 10mWT and 6MWT with a strong negative correlation, *r* =-0.910 between these outcome measures. This correlational result means that the faster the time taken to complete the 10mWT, the lesser the distance walked in the 6MWT or vice versa.

Table 6 Pearson Correlation between FSS, 10mWT and 6MWT

	Pearson Correlation, r	Sig.
FSS and 10mWT	0.173	0.610
FSS and 6MWT	-0.138	0.745
10mWT and 6MWT	-0.910	0.002

Sig. = Significance probability

6.0 Discussion

This present study analysis, based on a quantitative primary study of gait in MS, aims to recreate understanding of the effect of time of day and the between-day reliability of gait kinematics and walking performance in pwMS. This secondary analysis study also aims to report of the relationship between perceived fatigue and walking performance. The primary study is believed to be the only study to have investigated multiple walking tests outcomes and performed between-day AM and PM test-retest over a counter-balanced methodology. There has been considerable debate regarding gait kinematics and the probable association to fatigue in pwMS. The debatable evidences and the prevalence of fatigue in the MS population, warranted these aims. In addition, the various fatigue scoring measures available do not evidently explain gait variability, thus, any expression of quantifying this possible relationship, are in our interest to investigate.

6.1 Gait kinematics and walking performance in pwMS: differences between morning and afternoon

PwMS are thought to be prone to experiencing increased fatigability as the day progresses and as their activities increases (Schwid et al. 2002). It is often a belief that pwMS perform or function lesser in the afternoons and when tired. In our study, the measured ROM, speed, time and distance showed decreasing values from the AM to PM assessments. For any increase that was observed (rmaxpf and 10mWT), the increase was negligible. This may allocate the impression that with increasing physical demand or fatigue, walking kinematics may be altered. Likewise, in literature, walking kinematics may correspondingly be expressive of ambulatory capacity, and thus, we looked at the effect of time of day to gait changes in our study. Not many studies have investigated this outlook, whilst relatable available studies are repeatedly limited in generalizability by the wide representation of EDSS disability, small sample group or insufficient exploration of analysis: i.e. not reporting clinical relevance or MDC.

The AM and PM assessments of the 3D gait parameters and walking performance outcome measures in our study reported no statistical significant differences. This suggested that pwMS did not walk differently in the morning or afternoon, so no effect of time of day on gait capability. This finding is in line with a multi-centre study by Feys et al. (2014) who investigated 10mWT, 2-minute walk test (2MWT) and 6MWT in a large sample size of 102 subjects to determine the within-day variability of speed and performance in short (10mWT) and long (2MWT and 6MWT) walk tests. The outcomes were tested at 3 specified time intervals between morning, noon and afternoon and consisted of fast and usual walking pace. Our interest was in the finding from their study that walking assessment at usual speed increased variability with disability level and showed large within day variability, while the longer 6MWT showed smaller within-day variability. With regards to time of day, they reported that walking variability remained consistent between morning, noon and afternoon. Here it proposes that walking capability can be influenced by factors of disability, distance walked or ambulatory speed achieved upon walking and not due particularly to the time of day. This may be a logical reasoning to the non-significant results in our study.

Few studies have explored for variability of gait assessments by looking into the potential for time of day to influence differences in walking patterns. Morris et al. (2002) in their study of 14 participants and 14 matched control subjects, measured morning to afternoon gait consistency with four 10-meter gait trials repeated twice on the same day. The study found that MS patients walked slower and showed twice as much variability in gait compared to the normal participants. Importantly, the study reports statistical significance of morning and afternoon measurements but was recognized to be of non-clinical significance. Their study states that despite the perception by pwMS that they are tired or more lethargic in the afternoon, no justifiable evidence was found to support for alterations in walking and physical performance. Although it is likely that the small sample size in our study failed to detect important changes between the tests, but these mentioned studies dispute the belief that pwMS perform more poorly in the afternoon than in the morning. With MS having considerable impact on gait, knowledge of this time of day differences may be considered an important aspect still needing clarification in future MS research.

6.2 Test-retest reliability of 3D gait outcome measures

The test-retest reliability analysis was performed to measure the level of consistency between the morning measures and afternoon measures obtained from the between-day assessments of the gait outcome measures. The test-retest analysis in our study only involved the 3D gait analysis measures and the 10mWT walking performance test. This is probably due to people limitation which resulted in only few participants completing the 6MWT test. As reported by the 2-way random ICC analysis, moderate to good reliability of gait kinematics (ICC 0.50-0.97) and the 10mWT (ICC 0.95-0.97) was found. These measure analyses are evident statistically from findings in literature as discussed below.

Referring back to the study by Morris et al. (2002) as referred above, the authors performed a repeated measures analyses of variance test (ANOVAs) to analyse gait kinematics, which also examined the consistency for walking performance measured in a single day. Correlation t-tests was used where ANOVA showed significance to identify the differences between groups or across occasions of testing. The results of gait variables were found consistent throughout the different assessed time of day. Being the first study to report test-retest of gait in pwMS, their findings show high degree of repeatability in gait performance over the measured intervals. This study is however limited to single day test-retest and translated against our study with caution. Besides, there are very few studies reporting for between-day test-retest and especially for pwMS, therefore limits further exploration for comparisons with our study results.

In a systematic review by Andreapoulou et al. (2018) aimed to identify and synthesize literature of psychometric properties for walking performance and lower limb function, reports on reliability of the 10mWT was assessed for methodological quality using the COSMIN checklist. The review informed of the 10mWT being reliable outcome measure owing to the good test-retest values with ICC ranging >0.70. One of the studies mentioned in their review is a study by Paltamaa et al. (2008) that presented a test-retest ICC finding of 0.91 for the 10mWT outcome measure. The study involved 19 subjects with MS and the retest interval was one week apart to allow for between-day retest reliability. In a separate systematic review by Kieseler and Pozzilli (2012), the 10mWT and a variety of walking performance outcome measures when assessed for reproducibility across pwMS indicated that 10mWT is highly reproducible. The walking outcome quantified ICC of 0.81-0.96 within the 95% CI and SEM of 0.09 m/s following the analysis of test-retest reliability.

Apart from the 10mWT, the 3D gait analysis was also analysed for test-retest in our study. Findings demonstrated moderate to high ICC for this outcome parameters inclusive of hip ROM, ankle ROM and speed. In literature, there is lack of studies in the field of MS addressing reliability and validity of the 3D gait analysis. The review by Andreapoulou et al (2018) also highlighted that the 3D gait analysis used in assessing walking outcomes in pwMS, lacked in psychometric evidences. Hence, in our study, assessment of the test-retest reliability of gait parameters acquired from the 3D gait analysis hoped to provide as a pilot to design larger studies in filling this gap. Secondary to that, the sample size in our study may be questioned as too small to provide a real estimate of the reliability testing. Therefore, these findings should be interpreted with care and further research on the properties of 3D gait analysis is necessary.

Additionally, knowledge of SEM and MDC as in this study forms the basis for interpretation of a desirable outcome. The reports of SEM in our study analysis were low for all outcomes with the smallest SEM recorded for speed. MDCs based on 95% CI were also reported to provide for estimating reliable change in the measures. Our findings indicate reliability and precision in the measures obtained; allowing for the interpretation that the 3D gait analysis and 10mWT have acceptable random measurement error and good test-retest reliability. Although the reporting of SEM and MDC in literature has been encouraged, studies reporting these statistical estimates are sparse for gait outcome measures in MS. For that reason, our study and the specifics of SEM and MDC may contribute knowledge to this existing insufficiency.

6.3 Relationship between fatigue and walking performance outcomes

In examining for this relationship, our study found no significant correlation of perceived fatigue to the walking outcomes; 10mWT and the 6MWT. Perceived fatigue and its association with walking capabilities in pwMS is unclear and this relationship was examined recently by Kalron (2016). In his study of 124 MS participants, individuals in the fatigued group walked significantly slow with shorter step length and prolonged double support time. Fatigue was significantly correlated with 10/14 spatiotemporal parameters of gait, with P-value from Spearman's rho correlation highest at 0.99. His study continued to find that the strongest correlation of perceived fatigue is with speed (-0.339) and is supported by findings of Sacco et al. (2011) and Motl et al. (2012). As gait speed is the measurement outcome for walking performance, we estimated that there would be significant correlation between fatigue and walking outcome measures. Our study however found no statistical significance between fatigue and the gait outcome measures.

In our study, pwMS completed several trials of outcome measures in a day which we anticipated the probability of reporting for increased fatigue. We supposed that higher energy cost in walking may associate with greater perceived fatigue and trigger walking disturbances in pwMS but failed to demonstrate so. A population of pwMS was tested in induced fatigue condition by McLoughlin et al. (2016) and found walking induced fatiguability affects gait parameters. Findings of the paired t-test from their study showed that pwMS experienced a significant increase in exertion level in the last minute of the 6MWT ($p<0.01$). The study methodology used a modified 6MWT and assessed fatigue using a Visual Analogue Scale for Fatigue (VAS-F) evaluated pre- and post- to each 6 minute test. This study's methodology of assessing for fatigue represented a better evaluation for correlation of fatigue and walking than in our study. As fatigue score was not the main concern in the primary study, fatigue was only recorded once throughout the day tests in the study. This single fatigue assessment may not have had a strong effect in representing its correlation upon analysis to the 10mWT and 6MWT used.

In favour with Morris et al. (2002), our study findings suggest that changes in fatigue do not strongly correlate with changes in walking performance. In available studies, associations between self-reported fatigue and reduced walking speed or performance have been noted, but, these alterations in walking are more likely to be associated with motor impairments than fatigue by itself (Huisinga et al. 2011). An example of this is a study by Kelleher et al. (2010) who rationalizes that the power for push off to propel forward in walking is strongly determined by ankle PF by which step length and speed is generated. Reduced knee flexor and extensor strength and poor balance are other factors limiting gait speed (Yahia et al. 2011). This is relatable to our study, as lesser active ankle PF and hip ROM may have influenced the speed measurements reported from the 3D gait analysis.

Although typical for fatigue to be progressive in nature, Schwid et al. (2002) carries on to inform that besides physical activity, fatigue can be triggered by any other factors such as pain, illness and sleep quality. Fatigue ratings may also be affected by individual's performance and self-efficacy at the time of reporting. A most recent study by Dalgas et al. (2018), which also is the first study to examine the relationship between subjective walking ability and MS fatigue impact; marked a progress in deducing new observations pertaining to how miscellaneous psychological factors influence perceived walking ability. Their study observed that subjective assessments of walking ability showed stronger relationship to self-reports of fatigue than with objective measures of walking such as the 10mWT and 6MWT. These studies and their findings further explain that there is no immediate effect of fatigue on walking but may be an indirect resonance of multiple factors. In our study, we were not able to gather information on the initial physical activity status or well-being of the participants from the primary study, thus restricted our understanding of other possible factors that may well have affected the FSS scoring and the relationship finding.

The same Pearson Correlation results as well showed strong negative correlation between the two walking performance tests in our study. This is supported in literature by Dalgas et al. (2012) and Kieseier and Pozzilli (2012) that short and long walking tests are strongly correlated. These studies referred the short 10mWT to walking effort, therefore, expected to be associated with muscle strength; whilst the long 6MWT with walking endurance. White (2004) stated that muscle strength deficit in pwMS may result in limited ability to engage in physical exercise of sufficient intensity and duration. With this, we assume the significant negative correlation found in our study wherein increased fatigue causes reduced walking capacity. Similarly, the strength of this correlation can be explained alongside the understanding that the 10mWT and 6MWT are outcome measures of comparable characteristics. Both outcome measures are used clinically to assess walking capacity and also identify improvement or deterioration in walking. Knowing that the 10mWT and 6MWT measures elements of physical function, findings of our study can be supported; hence the strong correlation.

6.4 Limitations of the study and implications for future research

There are some limitations to the study, and these include limitations acknowledged from the primary study and in this current study. Being a secondary data analysis study, some disadvantages and limitations may be existing; such as no control over the primary study data and methodology, incomplete available information and may not contain sufficient information to testify for the present desired research purpose.

The most prominent limitation, which has been mentioned above, is the small sample size used. It is not clearly known why this limitation was present in the primary study, but, in our study, we selected only data of participants with sufficient readings for each outcome trial. A larger sample size would have made the findings from the data much more reliable as it would have increased the power of our analyses. Moreover, it would have allowed the inferences from the statistical analyses to be more applicable to the MS population. An appropriate measure of analysis we specified in our small sample sized study was the SEMs which supplemented for meaningful value of significance reporting. Reporting of SEM is broadly advocated in research and should be typically informed in future studies. One viable way to increase the sample size is to perform a widespread recruitment process which could yield more participants. Also, as the study design requires multiple visits to the gait analysis laboratory, probably provision of transport or reimbursement for travel fees might deny reluctance to travel and facilitate participation. This would however elicit the need for bigger research funding and greater time management.

Next is the limitation that the morning and afternoon assessment sessions were not adequately divided to represent AM and PM as separate measurements. The span between these sessions were not marked and may have affected our findings aimed at demonstrating effect of time of day on walking. Ideally, a gap of 6-7 hours separation to distinguish morning between afternoon time of day is advised. Therefore, we propose that future studies fix the time frames for morning and afternoon sessions, allowing sufficient gap to identify clearly for any differences in AM vs. PM walking. There were also no reports of amount of walking or physical activity done prior to attending each assessment session, nor records of physical fitness documented for each participant. These are amongst the insufficient details detected from the primary study data. We only noted from the primary study that rest was permitted if needed before and between each trial. The type of MS specific, EDSS specific, level of physical fitness and amount of physical activity performed may have underlying influence on measures of walking performance and level of perceived fatigue, and so, needs to be informed in detail. The ease with such precision may allow transferability of the study findings for potential research.

In terms of study methodology, the sole FSS fatigue score used and assessed once throughout the initial study seemed insufficient in representing our study's correlation analysis with walking performance. With fatigue being a variable of interest in our study, we were restricted in terms of analysing the true relationship of fatigue and walking capacity. The FSS mainly addresses expressions of fatigue in different domains of activity such as carrying out duties, work and physical functioning. The outcome also assesses how fatigue interferes with social life and affects motivation. With regards to the characteristics of FSS, the one-time assessment of fatigue in this study puts the accuracy of participants responses into question as it can be reported within the influence of anything at all, and not purely the feeling of fatigue following the walking trials. Thus, it is recommended that in future studies, an individualised fatigue likert scale before and after each walking assessment be used in addition to the FSS. This type of assessment is simple and may provide immediate response of feeling fatigue with each assessment trial. On another note, with the understanding that self-reported fatigue measures by itself may not identify walking irregularities, it is credible that future studies take on the assessment of objective gait measures along with the fatigue scales to monitor such changes in pwMS, as implemented in the initial study.

In short, all these steps and suggested opinions should be notably regarded if further studies are to be conducted based on the findings of this study.

6.5 Implications to practice

The fact that most pwMS are diagnosed when they are young adults and are living a longer life span resulting from medical management advances, justifies the need for identifying ways to overcome possible limitations of gait affecting ADL participation. As HCPs and carers, we acknowledge that it is important for this population to get the best advice and treatment regime planned at the appropriate time of day. Such treatment regime should also be prescribed confidently to enhance rehabilitation potential and improve compliance to physical partaking. This study brought forward some interesting findings which may relate to current circumstances especially in rehabilitative management.

Firstly, the finding of this study informed of no distinguishable difference in gait kinematics and walking performance of pwMS assessed in AM and PM sessions. This may advise that time of day do not alter pwMS walking ability. This is in contrast to their common thinking that they are less functional as the day goes by. With further evidences on this topic, hopefully pwMS will have a changed perspective on this common belief and build up not only physical strength through enhanced rehabilitative measures; but also, mental strength to overcome the fear of fatigue symptom.

Next, the findings of good between-day reliability for the gait outcome measures in this study is regarded as a start off for future research to address the psychometric properties of clinical outcome measures applicable for pwMS. The between-day retest reliability also allows for the reporting of clinically meaningful comparisons taking into account possible longitudinal changes of pwMS over a longer period of time.

Lastly, the identified poor relationship between self-perceived fatigue and walking performance in pwMS suggested that the psychological influences or subjective perceptions may not necessarily define the physical capability of pwMS. This finding along with more research hoped to recreate an understanding in pwMS to do away with limitations of perceptions, which may then substantially support for better physical participation.

7.0 Conclusion

In summary, this paper suggested that there is no effect of time of day on walking in pwMS. Our results appear to be supported by studies that concluded no justifiable evidence supporting differences in gait kinematics and walking capacity assessed in different times of day. Nevertheless, we observed from the collected data, a decline in measurements of ROM and distance walked in the PM compared to the AM recordings. This finding is valuable in light of arguing for what is observed and expressed amongst pwMS in society and in care participation. Yet, the limitation of this small size study probably inhibited assumption of significant inferences about this prediction that pwMS do no walk differently in the mornings as to the afternoons.

This study's results on test-retest reliability of the 3D gait analysis and the 10mWT informed that these outcome measures are reasonably reproducible on repeated measures. The 10mWT especially is highly reproducible and this conclusion follows from the supporting fact that previous studies report high ICCs of the 10mWT in pwMS. As discussed and to our knowledge, there are limited studies exploring between-day test-retest analysis of the 10mWT; and no studies have yet reported reliability of the 3D gait analysis outcome measure in pwMS. The psychometric properties of 3D gait analysis need future consideration and research in MS. Importantly, these reliability findings add to the knowledge gap in research and provides information constructive for larger confirmatory studies.

This study continued to measure for possible relationship between self-reported fatigue and walking performance. This was done through correlation statistics and found weak association with no statistically significant correlation between these measures. It was assumed that perceived fatigue levels in pwMS may perhaps affect walking function, but, the findings did not demonstrate for evidence. The limitation of the primary study methodology and variation in fatigue symptom may be reasons for this lack of correlation. Nevertheless, a strong negative correlation was found between the 10mWT and 6MWT. This strong correlation is as supported in literature confirming that these two gait outcome measures are significantly associated. This study also interprets the negative correlation between the 10mWT and 6MWT to be inductive for future researches aim and hypothesis.

The results of this study go some way to comprehend the knowledge of time of day, perceived fatigue in pwMS and the relatedness to walking. Future research on these outcomes might extend the explanations of the cause and effect of MS on walking capacity in the MS population.

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